Technical Report # 185

STRUCTURAL IDENTIFICATION OF LARGE SYSTEMS BY REDUCTION TO SUBSYSTEMS: VLDL TRIGLYCERIDES

by

J. Eisenfeld[1] and S. M. Grundy[2]

[1]Department of Mathematics
University of Texas at Arlington
Arlington, Texas 76010

[2]Center for Human Nutrition
University of Texas Health Science Center at Dallas
5323 Harry Hines Boulevard
Dallas, Texas 75235

May, 1982

1. INTRODUCTION Experiments are performed for identification purposes, i.e. to identify the values of unknown paprameters from data. In the event that one or more parameters can not be identified, the cause could be the result of a variety of problems: insuffcient or infrequent sampling, random or nonrandom disturbances, numerical ill-conditioning and etc. The input-output configuration may also be the cause of non-identifiability. In other words, even if the sampling and numerical procedure could be carried out under the most ideal conditions, certain parameters may not be identifiable because these parameters are not uniquely contained in the transfer function, in which case these parameters are said to be not structurally identifiable [1].

During the past decade a variety of criteria have been established in order to test the structural identifiability properties of parameters for a general compartmental system. (See [2-9] and references therein.) These tests are analytical, requiring only the model, the set of unknown parameters and the input-output configuration. Since actual data is not required, these structural identifiability tests should be performed prior to the planned experiment in order to determine if identifiability is at least possible. In other words, the most appropriate time to consider structural identifiability is during the planning stages of the experiment.

With the advent of the better sampling techniques, sophisticated computer technology, and improved numerical procedures, biological models are becoming increasingly larger and more complex. However, the analytical methods (by themselves) become computationally unfeasible as the structure to be examined increases in complexity. The problems arising from large systems are becoming a major issue in the theory of structural identifiability. One approach to this problem is computerisation of the existing methods [2,3]. Another approach is to decompose the large system into smaller systems [4,5]. This paper uses the latter approach. Of course, there are a multitude of ways of decomposing a system into subsystems and a variety of techniques can be employed to take advantage of the decomposition.

The basic idea, to be presented here, is to represent the system as two systems in series (Figure 1) or as two subsystems in parallel (Figure 2). In either case the transfer function Φ is a combination (a product or a sum) of the transfer functions $\Phi^{(i)}$ $(i = 1,2)$ of the constituent subsystems. So the problem is to obtain necessary and sufficient conditions for structurally identifying the constituent transfer functions. Of course the constituent subsystems may be further decomposed.

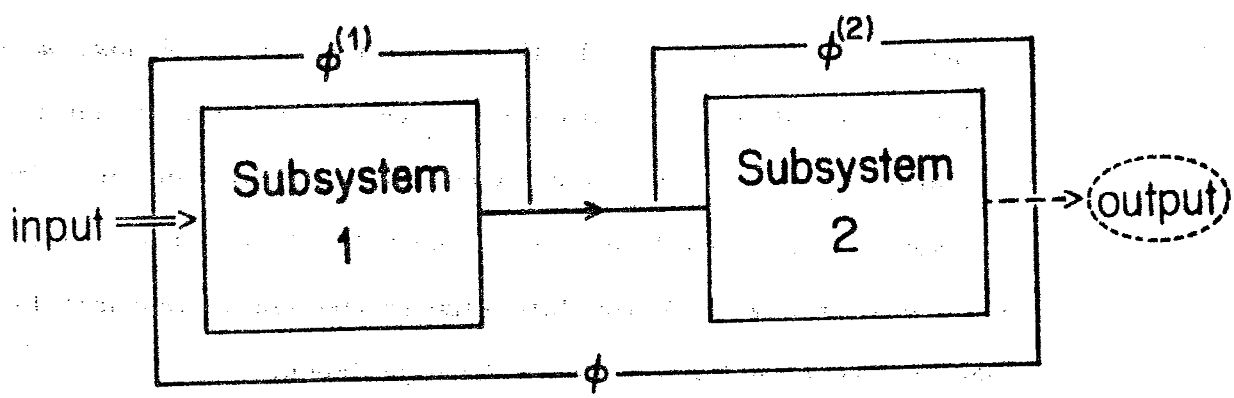

Figure 1. Subsystems in series: $\Phi = \Phi^{(2)}\Phi^{(1)}$

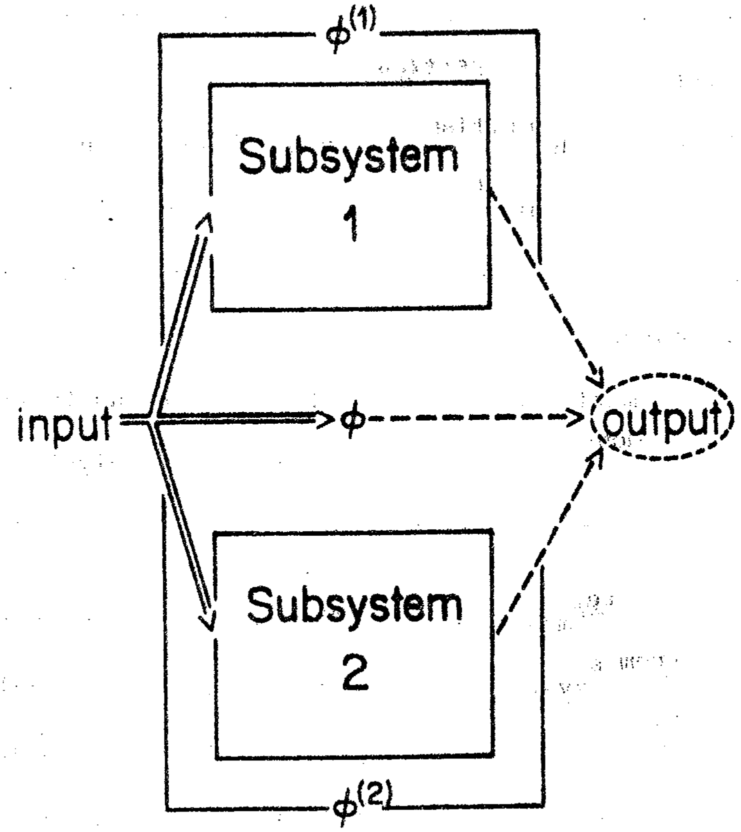

Figure 2. Subsystems in parallel: $\Phi = \Phi^{(1)} + \Phi^{(2)}$.

The main purpose of this paper is to formulate criteria for decomposing a large system into subsystems in such ways as to be able to determine the identifiability properties of parameters, with respect to the large system, by their identifiability properties, with respect to the subsystem in which they are contained. These criteria will be illustrated by applying them to the model which is used to describe the kinetics of Very Low Density Lipoprotein Triglycerides.

Being primarily concerned with applications to tracer and drug studies, we use the nomonclature from compartmental analysis, however the results apply in generality to the class of linear time-invariant systems.

2. Problem statement, definitions, and preliminary results

A. Concept from systems theory and compartmental analysis

We consider a first-order perturbation experiment with n_B test inputs u_r, and n_C measurement outputs y_m, on an n-compartmental system in a constant steady state. The set of equations representing the dynamics of the deviation x_i, of the generic i th compartment from its steady-state value and of the relations between such deviations and measurements is linear and time-invariant [10]:

$$\dot{x}_i = -\sum_{j=0}^{n} a_{ji}x_i + \sum_{j=1}^{n} a_{ij}x_j + \sum_{r=1}^{n_B} b_{ir}u_r \quad (i=1,2,\ldots,n),$$

$$y_m = \sum_{i=1}^{n} c_{mi}x_i \quad (m=1,2,\ldots,n_C),$$

or, in the usual system-theory matrix form,

$$\underline{\dot{x}} = A\underline{x} + B\underline{u},\ \underline{x}(0) = \underline{0},\ \underline{y} = C\underline{x}, \tag{2.1}$$

where $\underline{x}$ is the <u>state vector</u> formed by the n variables x_i, $\underline{u}$ is the <u>input vector</u> formed by the n_B inputs (including instantaneous (delta function) inputs), $\underline{y}$ is the <u>output vector</u> formed by the n_C experimental measurements, B is the $n x n_B$ <u>input matrix</u> of elements b_{ir}, C is the $n_C x n$ <u>output matrix</u> of elements c_{mi}, and A is the nxn <u>compartmental matrix</u> of <u>fractional transfer coefficients</u>, $a_{ij} (i \neq j)$, and $a_{jj} = -\sum_{\substack{j=0 \\ j \neq i}} a_{ij}$

(a_{0j} denotes the fractional transfer from j to the environment).

The dynamical system (2.1) is characterized by its <u>transfer function (matrix)</u>,

$$\Phi(s) = C(sI-A)^{-1}B, \tag{2.2}$$

where s is the <u>Laplace transform variable</u> and I generically denotes an identity matrix. An identity which is useful in connection with the transfer function is [11]

$$(sI-A)^{-1} = R(s)/\Delta(s), \tag{2.3}$$

where

$$\Delta(s) = \det(sI-A)^{-1} = s^n + \delta_{n-1}s^{n-1} + \delta_{n-2}s^{n-2} + \ldots + \delta_0. \tag{2.4}$$

is the <u>characteristic polynomial</u> and

$$R(s) = (s^{n-1}+\delta_1 s^{n-2}+\ldots+\delta_{n-1})I + (s^{n-2}+\delta_1 s^{n-3}+\ldots$$
$$+ \delta_{n-1})A + \ldots + (s+\delta_1)A^{n-2} + A^{n-1}. \tag{2.5}$$

Premultiplying and postmultiplying in (2.5) by C and B, respectively, we obtain

$$\Phi(s) = P(s)/\Delta(s), \tag{2.6}$$

where

$$P(s) = CR(s)B. \tag{2.7}$$

Each entry in the transfer function is a ratio of polynomials,

$$\phi_{ij}(s) = p_{ij}(s)/\Delta(s). \tag{2.8}$$

If $\Delta(s)$ has a monomial factor which is a common factor of all $p_{ij}(s)$, $i = 1,2,\ldots,n_C$, $j = 1,2,\ldots,n_B$, then $\Phi(s)$ is <u>reducible</u>; otherwise it is <u>irreducible</u>. The system (2.1) is reducible or irreducible according to whether or not its transfer function is reducible or irreducible.

<u>Example 2.1</u> The system in Figure 5, Section 5 arises from decomposing the larger system, Figure 3. The transfer function corresponding to Figure 5 (see Example 4.1) is

$$\Phi(s;\underline{\theta}) = \frac{\theta_4\theta_6\theta_7\theta_8\theta_9\theta_{10}}{(s+\theta_6)(s+\theta_7)(s+\theta_8)(s+\theta_9)(s+\theta_{10})} + \frac{\theta_5\theta_{11}}{s+\theta_{11}} \tag{2.9}$$

($\underline{\theta} = (\theta_4,\theta_5,\theta_6,\theta_7,\theta_8,\theta_9,\theta_{10},\theta_{11})$ is the parametrization vector.) The characteristic polynomial, $\Delta(s;\underline{\theta})$, is the product of the six monomials appearing in (2.9). Let $q(s;\underline{\theta})$ be the least common multiple of these monomials. Then $q = \Delta$ if and only if

$$\theta_{11} \neq \theta_k,\ k = 6,7,8,9,10. \tag{2.10}$$

Thus condition (2.10) is necessary and sufficient for irreducibility.

<u>Remark 2.1</u> The irreducibility conditions (2.10) are satisfied at all points in the eight dimensional parameter space except on the lower dimensional hyperplanes, $\theta_{11} = \theta_k$, $k = 6,7,8,9,10$. Thus $\Phi(s;\theta)$ is irreducible <u>almost everywhere</u>. This fact is deduced more easily from input-output connectability and related criteria [7,8]. We shall say more about the almost everywhere property in Remark 3.1.

The system (2.1) is CC (completely controllable) if its controllability matrix $U = [B, AB, \ldots, A^{n-1}B]$ is of full rank (i.e. UU' is nonsingular); it is CO(completely observable) if its observability matrix $V = [C', A'C', \ldots, (A')^{n-1}C']$ (" ' " means transpose) has full rank. We will require the following well-known result ([12];[13],[6]).

Lemma 2.1 A system is irreducible if and only if it is both CC and CO.

Example 2.2 The system in Figure 4 arises from decomposing the larger system, Figure 3. In this case

$$C, A, B = (1,0), \begin{pmatrix} -(\theta_2+\theta_3+\theta_4+\theta_5) & \theta_1 \\ \theta_2 & -\theta_1 \end{pmatrix}, \begin{pmatrix} 1 \\ 0 \end{pmatrix},$$

which gives $\det U = \theta_2$, $\det V = \theta_1$. Since θ_1, θ_2 are nonzero parameters this system is irreducible.

The matrices which appear in $P(s)$ (formulas (2.7), (2.5)) are the $n_C \times n_B$ matrices

$$M_k = CA^kB, \ k = 0,1,\ldots \ . \tag{2.11}$$

They are called the Markov matrices, or the Markov parameters in the case $n_C = n_B = 1$. The following result is well known [6].

Lemma 2.2 All the Markov matrices (2.11) are uniquely determined from the transfer function. Conversely, the Markov matrices, M_k, $k = 0,1,\ldots,2n-1$ (the first $2n$ suffice) uniquely determine the transfer function.

B. Structural Identifications

We consider a planned experiment. We know, a priori, that (for a non-resonant system) the transfer function will have the form [6]

$$\Phi(s) = \sum_{k=1}^{r} D_k/(s+\pi_k), \tag{2.12}$$

where the D_k and the π_k are estimable from input-output data, without regard to system parameters. We call the function defined by formula (2.12) the measured transfer function. On the other hand, a formal expression for the transfer function is obtained from formula (2.2); however, the matrices which appear in this formula are given in terms of a parameter vector $\underline{\theta}$, and so the parameterized transfer function is

$$\Phi(s;\underline{\theta}) = C(\underline{\theta})(sI-A(\underline{\theta}))^{-1}B(\underline{\theta}). \tag{2.13}$$

The structural identifiability problem consists of establishing whether or not $\underline{\theta}$, or a single parameter θ, can be determined from the relationship

$$\Phi(s;\underline{\theta}) = \Phi(s). \tag{2.14}$$

By a single parameter, we mean a constituent θ_i of θ or a lumped combination of the θ_i. The dimension of $\underline{\theta}$ is assumed minimal; there are no relations between the θ_i.

There are several useful definitions of structural identifiability, each carries a particular point of view [9]. Some of these are given below.

(i) Unique identifiability (also called global identifiability). The single parameter, θ, is said to be uniquely identifiable (from the transfer function) if there exists a unique solution for θ satisfying equation (2.14). If all components θ_i of the parameter vector $\underline{\theta}$ are uniquely identifiable then the model is said to be parameter identifiable.

Example 2.3 Formula (2.13), applied to the system in Example 2.2, yields

$$\Phi(s;\underline{\theta}) = (s+\theta_1)/[s^2+(\theta_1+\theta_2+\sigma)s+\theta_1\sigma], \tag{2.15}$$

where $\sigma = \theta_3 + \theta_4 + \theta_5$. Since the 2-compartmental system is irreducible (Example 2.2) the measurable transfer function has the form $\Phi(s) = D_1(s+\pi_1) + D_2/(s+\pi_2)$ (the π_i are distinct (see [14])). Equation (2.14) yields, $\theta_1 = D_1\pi_2 + D_2\pi_1$, $\theta_1 + \theta_2 + \sigma = \pi_1 + \pi_2$, $\theta_1\sigma = \pi_1\pi_2$. Consequently, θ_1, θ_2, and σ are uniquely identifiable.

(ii) Identifiability (also called local identifiability). If there does not exist a unique solution for a particular parameter but there is at most finitely many solutions, as in Example 2.4 (below), then it may still be possible to ascertain the appropriate solution, say, from a priori knowledge of the parameter's range. Therefore, the following definition is useful. The single parameter θ is said to be identifiable if there exists at most finitely many solutions for θ satisfying equation (2.14). If all θ_i are identifiable the model is said to be system identifiable.

Example 2.4 We return to Example 2.1. Assuming irreducibility (it will be shown later that this condition is not necessary) the measurable transfer function has the form, $\Phi(s) = E/(s+\pi_3)(s+\pi_4)(s+\pi_5)(s+\pi_6)(s+\pi_7) + D/(s+\pi_8)$. Equating this expression to expression (2.9) obtains $\theta_{11} = \pi_8$ and the equality between sets: $\{\theta_6, \theta_7, \theta_8, \theta_9, \theta_{10}\} = \{\pi_3, \pi_4, \pi_5, \pi_6, \pi_7\}$. Each θ_k, except θ_{11}, has five possible solutions; thus θ_k is identifiable but it is not uniquely identifiable, while θ_{11} is uniquely identifiable. Finally, θ_4 is identifiable and θ_5 is uniquely identifiable from the relationships: $\theta_4 = E/(\theta_6\theta_7\theta_8\theta_9\theta_{10})$, $\theta_5 = D/\theta_{11}$ (the θ_i are nonzero parameters).

It is interesting that this system is identifiable whether or not the irreducibility condition (2.10) is satisfied (see Example 4.2). The example is among many examples which show that irreducibility is not necessary for identifiability [6].

(iii) Identifiability from a constituent function. Suppose that the (measurable and parameterized) forms of the transfer function is expressed in terms of two other functions, e.g., $\Phi = \Phi^{(2)}\Phi^{(1)}$ or $\Phi = \Phi^{(1)} + \Phi^{(2)}$, as depicted in Figures 1 and 2. The relationship is denoted by

$$\Phi(s) = F(f(s),g(s)), \quad \Phi(s;\underline{\theta}) = F(f(s;\underline{\theta}),g(s;\underline{\theta})). \qquad (2.17)$$

A constituent function, f, of the transfer function is said to be identifiable (resp. uniquely identifiable) if there exist at most finitely many solutions (resp. a unique solution) for f from the relationship $\Phi(s;\theta) = \Phi(s)$.

The single parameter θ is said to be identifiable (resp. uniquely identifiable) from the constituent function, f, if there are at most finitely many (resp. a unique solution) for θ from the relationship, $f(s;\underline{\theta}) = f(s)$.

The following results should be apparent from the above definitions.

Lemma 2.3 Suppose that a constituent function, f, is identifiable (resp. uniquely identifiable) and that a single parameter θ is identifiable (resp. uniquely identifiable) from f, then θ is identifiable (resp. uniquely identifiable).

Lemma 2.4 The characteristic polynomial, Δ, and the polynomial, P, (which constitute the transfer function as given in formula (2.6)) are both uniquely identifiable constituent functions, provided that the system is irreducible.

3. Systems in series In this section we consider a system whose flow diagram is depicted in Figure 1. To be precise we need to distinguish compartments in terms of the input-output relations. Consider the dynamical equations, (2.1). A compartment k is said to be an input compartment if $b_{kj} \neq 0$ for at least one index j; it is said to be an output compartment

if $c_{ik} \neq 0$ for at least one index i. We also distinguish the compartments in terms of the direction of flow within the system. A compartmental system is said to admit a T-R (transmitter-receiver) decomposition if the compartments can be separated into disjoint sets, T, the transmitters and, R, the receiver, such that

$$a_{tr} = 0, \; t \in T, \; r \in R. \tag{3.1}$$

The system (2.1) is said to be in series if it admits a T-R decomposition such that no transmitter compartment is an output compartment, i.e.,

$$c_{it} = 0, \; t \in T, \; i = 1,2,\ldots,n_C, \tag{3.2}$$

and no receiver compartment is an input compartment, i.e.,

$$b_{rj} = 0, \; r \in R, \; j = 1,2,\ldots,n_B. \tag{3.3}$$

In other words, a system is in series if and only if the compartments can be numbered in such a way that the matrices A, B, and C can be partitioned:

$$A = \begin{bmatrix} A^{(1)} & 0 \\ E & A^{(2)} \end{bmatrix}, \; B = \begin{bmatrix} B^{(1)} \\ 0 \end{bmatrix}, \; C = \begin{bmatrix} 0, C^{(2)} \end{bmatrix}. \tag{3.4}$$

Here "0" generically denotes a matrix of zero entries, $A^{(1)}$ (resp. $A^{(2)}$) is the $n^{(1)} \times n^{(1)}$ (resp. $n^{(2)} \times n^{(2)}$) compartmental matrix whose elements are the fractional transfer coefficients from transmitter to transmitters (resp. receivers to receivers), E is the $n^{(2)} \times n^{(1)}$ matrix whose elements are the fractional transfer coefficients from transmitters to receivers, $B^{(1)}$ is an $n^{(1)} \times n_B$ (input) matrix and $C^{(2)}$ is an $n_C \times n^{(2)}$ (output) matrix.

Lemma 3.1 If a system is in series then the transfer function is a product of constituent transfer functions, i.e., it is expressible in the form:

$$\Phi(s) = \Phi^{(2)}(s)\ \Phi^{(1)}(s), \tag{3.5}$$

where

$$\Phi^{(k)}(s) = C^{(k)}(sI-A^{(k)})^{-1}B^{(k)},\ k = 1,2 \tag{3.6}$$

<u>Proof.</u> Substituting (3.4) into (2.2) obtains

$$\Phi(s) = C^{(2)}(sI-A^{(2)})^{-1}E(sI-A^{(1)})^{-1}B^{(1)}. \tag{3.7}$$

The representation (3.5) - (3.6) results from factoring E,

$$E = B^{(2)}C^{(1)}. \tag{3.8}$$

(Such a factoring always exists, say by taking one of the factors to be the identity matrix.)

From the point of view of structurial identification, the representation (3.5) - (3.6) is not of interest unless the constituent transfer functions are identifiable. For this reason we consider the case where the dimensions of $B^{(2)}$ and $C^{(1)}$ are $n^{(2)} \times 1$ and $1 \times n^{(1)}$, respectively, in which case

$$C^{(1)} = [c_1^{(1)},c_2^{(1)},\ldots,c_{n(1)}^{(1)}],\ B^{(2)}= [b_1^{(2)},b_2^{(2)},\ldots,b_{n(2)}^{(2)}]', \tag{3.9}$$

$$\Phi^{(1)} = [\phi_1^{(1)},\phi_2^{(1)},\ldots,\phi_{n_B}^{(1)}],\ \Phi^{(2)} = [\phi_1^{(2)},\phi_2^{(2)},\ldots,\phi_{n_C}^{(2)}]', \tag{3.10}$$

$$\phi_{ij} = \phi_i^{(2)}\phi_j^{(1)},\ i = 1,2,\ldots,n_C,\ j = 1,2,\ldots,n_B. \tag{3.11}$$

Now the question is, does ϕ_{ij} identify each of its factors, $\phi_i^{(2)}$ and $\phi_j^{(1)}$? The question can be considered in parts by writing formula (2.8) in the form

$$\phi_{ij}(s) = \gamma_{ij}e_{ij}(s)/\Delta(s) \tag{3.12}$$

where $e_{ij}(s)$ (and also $\Delta(s)$) is a <u>monic polynomial</u>, i.e. the leading coefficient is unity, and $\gamma_{ij} \neq 0$. Similarly,

$$\phi_\nu^{(k)}(s) = \gamma_\nu^{(k)} e_\nu^{(k)}(s)/\Delta^{(k)}(s), \tag{3.13}$$

where $e_\nu^{(k)}(s)$ is monic and $\gamma_2^{(k)} \neq 0$, $k = 1,2$. Substituting (3.12) and (3.13) into (3.11) yields the identities:

$$\gamma_{ij} = \gamma_i^{(2)}\gamma_j^{(1)}, \tag{3.14}$$

$$e_{ij}(s) = e_i^{(2)}(s)e_j^{(1)}(s), \tag{3.15}$$

$$\Delta(s) = \Delta^{(2)}(s)\Delta^{(1)}(s). \tag{3.16}$$

Consider the problem of solving for the factors $\gamma_i^{(2)}$ and $\gamma_j^{(1)}$ in terms of the γ_{ij} from the relations (3.14). In general, this problem is not solvable. However, if just one of the $n_B + n_C$ constants $\gamma_i^{(2)}$ and $\gamma_j^{(1)}$ is known, then the remaining constants are solvable. In fact if $\gamma_\mu^{(2)}$ is known then so are $\gamma_j^{(1)} = \gamma_{\mu j}/\gamma_\mu^{(2)}$, $j = 1,2,\ldots,n_B$,. Now fixing j, say $j = 1$, the remaining $\gamma_i^{(2)}$ are obtained from $\gamma_i^{(2)} = \gamma_{i1}/\gamma_1^{(1)}$. A similar argument applies if one of the $\gamma_j^{(1)}$ is known. Now suppose that one of the entries of the matrix $C^{(2)}B^{(2)}$ is nonzero, say it is the μth entry, τ_μ. It is clear from formulas (2.5) - (2.7) that τ_μ is the leading coefficient of $\phi_\mu^{(2)}(s)$, i.e. $\tau_\mu = \gamma_\mu^{(2)}$. Thus if one of the entries of $C^{(2)}B^{(2)}$ is nonzero and it is known then all of the $n_B + n_C$ constants, $\gamma_i^{(2)}$ and $\gamma_j^{(1)}$, are solvable from relations (3.14). This is also true if one of the entries of $C^{(1)}B^{(1)}$ is nonzero and known. The above observations are stated formally in Lemma 3.2.

<u>Lemma 3.2</u> The $n_B + n_C$ constants $\gamma_i^{(2)}$ and $\gamma_j^{(1)}$ are uniquely identifiable if either (i) one of the entries of $C^{(1)}B^{(1)}$ is nonzero and it is a priori known or (ii) one of the entries of $C^{(2)}B^{(2)}$ is nonzero and it is a priori known.

<u>Lemma 3.3</u> Suppose that the system is irreducible, then the $n_B + n_C + 2$ polynomials, $\Delta^{(k)}(s)$, $e_\nu^{(k)}(s)$, are identifiable.

<u>Proof.</u> Since the system is irreducible, $\Delta(s)$ and $P_{ij}(s)$, $1 \le i \le n_C$, $1 \le j \le n_B$ are uniquely identifiable (Lemma 2.4). Let $\pi_j^{(1)}$ be a root of $\Delta^{(1)}(s)$. Then, from (3.16), $\pi_j^{(1)}$ is a root of $\Delta(s)$; thus there are finitely many solutions for $\pi_j^{(1)}$. This being true for each root of $\Delta^{(1)}(s)$, $\Delta^{(1)}(s)$ is identifiable.

Similar arguments show that $\Delta^{(2)}(s)$ and the polynomials $e_\nu^{(k)}(s)$ are identifiable (recall that $P_{ij}(s)$ and $e_{ij}(s)$ have identical roots).

<u>Lemma 3.4</u> Suppose that there is a compartment f, called the <u>first receiver</u>, such that $f \in R$ and $a_{rt} = 0$ whenever $r \in R - f$ and $t \in T$. It is assumed, without loss of generality, that f is numbered first among the receivers. Then the matrices in (3.9) are:

$$C^{(1)} = [a_{f1}, a_{f2}, \ldots, a_{fn^{(1)}}], \quad B^{(2)} = [1,0,\ldots,0]'. \tag{3.17}$$

<u>Proof.</u> The hypothesis states that all rows of E are zero except for the first row, which is $[a_{f1}, a_{f2}, \ldots, a_{fn^{(1)}}]$. Clearly, $E = B^{(2)}C^{(1)}$, where $C^{(1)}$ and $B^{(2)}$ are defined in (3.17).

<u>**Example 3.1**</u> **We consider the system in Figure 5(b) (Section 5). The system has a $T - R$ decomposition where $T = \{10\}$ and $R = \{11,12,13,14\}$. The** matrices in formula (3.4) are

$$B^{(1)} = [\theta_4], \; C^{(2)} = [0,0,0,\theta_{10}]', \; A^{(1)} = [-\theta_6],$$

$$E = \begin{bmatrix} \theta_6 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad A^{(2)} = \begin{bmatrix} -\theta_7 & 0 & 0 & 0 \\ \theta_7 & -\theta_8 & 0 & 0 \\ 0 & \theta_8 & -\theta_9 & 0 \\ 0 & 0 & \theta_9 & -\theta_{10} \end{bmatrix}.$$

The system has a first receiver $f = 11$, and so $E = B^{(2)}C^{(1)}$, where $C^{(1)} = [\theta_6]$ and $B^{(2)} = [1,0,0,0]'$. By Lemma 3.4, $\Phi = \Phi^{(2)}\Phi^{(1)}$, where $\Phi^{(1)}(s) = \theta_4\theta_6/(s+\theta_6)$. Now the receiver constituent is also a system in series with a first receiver. In fact, Lemma 3.4 can be applied in succession to obtain

$$\Phi(s) = [\theta_4\theta_6/(s+\theta_6)][\theta_7/(s+\theta_7)][\theta_8/(s+\theta_8)][\theta_9/(s+\theta_9)][\theta_{10}/(s+\theta_{10})]. \tag{3.18}$$

where each term in brackets is a constituent transfer function. It is apparant from the form of (3.18) that the poles θ_k, $k = 6,7,8,9,10$ are identifiable and so is the constant $\theta_4\alpha$, where α is the product of the poles. Since α is identifiable, so is θ_4. Thus all six parameters are identifiable.

<u>Lemma 3.5</u> Suppose that there is a compartment, ℓ, called the <u>last transmitter</u>, such that $\ell \in T$ and $a_{rt} = 0$ whenever $r \in R$ and $t \in T - \ell$. It is assumed, without loss of generality, that ℓ is numbered last among the transmitters. Then the matrices in (3.9) are:

$$C^{(1)} = [0,\ldots,0,1], \; B^{(2)} = [a_{1\ell}, a_{2\ell}, \ldots, a_{n(2)\ell}]'. \tag{3.19}$$

<u>Proof.</u> The hypothesis states that all columns of E are zero except for the last column, which is $[a_{1\ell}, a_{2\ell}, \ldots, a_{n(2)\ell}]'$. Clearly, $E = B^{(2)}C^{(1)}$ where $C^{(1)}$ and $B^{(2)}$ are defined in (3.19).

<u>Example 3.2</u> We consider the system in Figure 7 (Section 5). It is a system in series with $\ell = 4$ as the last transmitter. The system decomposes

into a transmitter subsystem, Figure 4, and a receiver subsystem, Figure 5.

Proposition 3.1 Suppose that a system in series has the following properties.

1. There is either (a) a first receiver or (b) a last transmitter.
2. One of the conditions ((i) or (ii)) in Lemma 3.2 holds.
3. The system is irreducible.

Then the transfer function $\Phi = \Phi^{(2)}\Phi^{(1)}$, where the constituent transfer functions are given in formulas (3.6), (3.4) and (3.17), for the first-receiver case, or in formulas (3.6), (3.4), and (3.19), for the last-transmitter case. Moreover, the constituent transfer functions are identifiable.

Proof. The decomposition, $\Phi = \Phi^{(2)}\Phi^{(1)}$ follows from Lemma 3.1. To obtain the first-receiver form, (3.17), we apply Lemma 3.4 and the last-transmitter form, (3.19), follows from Lemma 3.5. The fact that the constituent transfer functions are identifiable is a consequence of Lemmas 3.2 and 3.3.

Example 3.3 We continue from Example 3.2. In the transmitter subsystem, Figure 4, there is a single input and a single output and both occur in compartment 4. Moreover, $C^{(1)}B^{(1)} = [1,0][1,0]' = 1$, so that the second condition in Proposition 3.1 is satisfied. Next we find the conditions under which Φ is irreducible. We recall that Φ_1 is (always) irreducible (Example 2.2) and Φ_2 is irreducible under condition (2.10)(Example 2.1). Let condition (2.10) be satisfied, then Φ is reducible if and only if a zero of one of the constituent transfer functions coincides with a pole of the other. Now $\Phi^{(1)}$ is given in formula (2.15) and $\Phi^{(2)}$ is given in formula (2.9). There are no cancellations between these functions if and only if:

$$\theta_1 \neq \theta_k, \ k = 6,7,8,9,10,11, \tag{3.20}$$

$$(\theta_{11}+\pi_i)\theta_4 \prod_{k=6}^{10} \theta_k + \theta_6\theta_{11} \prod_{k=6}^{10} (\theta_k+\pi_i) \neq 0, \ i = 1,2, \tag{3.21}$$

where π_1 and π_2 are the roots of

$$\Delta^{(2)}(s) = s^2 + (\theta_1+\theta_2+\theta_3+\theta_4+\theta_5)s + \theta_1(\theta_3+\theta_4). \tag{2.22}$$

In conclusion, $\phi^{(1)}$ and $\phi^{(2)}$ are identifiable as long as the irreducibility conditions, (2.10), (3.20), and (3.21) are satisfied.

Remark 3.1 The irreducibility conditions may not be easily deriveable, especially in large systems, and moreover, it may be difficult to determine, a priori, whether or not these conditions are satisfied. It is possible to avoid the issue by adopting the point of view that structural identifiable almost everywhere is a sufficient criteria, because, in this case, the chances of incurring a point at which the system is not structural identifiable (in an actual experiment) is negligible [7,8]. Towards this point of view, Proposition 3.1 may be modified to read as follows.

Proposition 3.2 If hypothesis (3) of Proposition 3.1 is changed to (3') the system is irreducible almost everywhere, then the conclusions of that proposition hold in the almost everywhere sense.

Moreover, irreducible almost everywhere criteria are less difficult to apply. For instance, in all the examples discussed above, the system satisfies the following conditions:

(1) Every compartment is input reachable.

(2) Every compartment reaches at least one output.

(3) The system is without traps.

Systems satisfying these three conditions are irreducible almost everywhere [7,8].

Remark 3.2 Even though one adopts the almost-everywhere point of view the irredicibility conditions are still of significance. For instance, some computer programs assume irreducibility (explicitly or implicity [18]). In such cases, numerical difficulties can arise (in the estimation problem) when in proximity to a point where irreducibility fails. The numerical difficulties become apparent when we expand the impulse response of the compartmental system as the exponential sum $D_1e^{\pi_1 t} + D_2e^{\pi_2 t} + \ldots + D_ne^{\pi_n t}$. If the order of the system is n then we expect to have n linearly independent terms, i.e. (i) the π_i are distinct and (ii) the D_i are nonzero. A necessary and sufficient condition for condition (i) and (ii) to hold is that the system is irreducible. As the parameter vector approaches a point where the irreducible conditions are violated then either some of the π_i coalesce or some of the D_i tend to zero; either one of these circumstances is apt to cause numerical difficulties in the parameter estimation problem.

4. Systems in parallel In this section we consider a system whose flow diagram is depicted in Figure 2. and which is described below.

The system (2.1) is said to be in parallel if its compartments can be separated into two disjoint subsets, $S^{(k)}$, $k = 1,2$, such that there is no flow between these subsets, i.e.,

$$a_{ij} = 0, \; i \in S^{(1)}, \; j \in S^{(2)}. \tag{4.1}$$

In other words, a systems is in parallel if and only if the compartments can be numbered in such a way that the compartmental matrix can be partitioned as

$$A = \begin{bmatrix} A^{(1)} & 0 \\ 0 & A^{(2)} \end{bmatrix}, \tag{4.2}$$

where $A^{(1)}$ and $A^{(2)}$ are submatrices of dimensions $n_1 \times n_1$ and $n_2 \times n_2$, respectively. We also partition B and C as

$$B = [B^{(1)}, B^{(2)}]', \; C = [C^{(1)}, C^{(2)}], \tag{4.3}$$

where $B^{(1)}$, $B^{(2)}$, $C^{(1)}$ and $C^{(2)}$ have respective dimensions $n_1 \times n_B$, $n_2 \times n_B$, $n_C \times n_1$, and $n_C \times n_2$. By substituting (4.2) - (4.3) into (2.2) we obtain the following result.

Lemma 4.1 A system in parallel has the property that its transfer function is expressible as a sum of constituent transfer functions,

$$\Phi(s) = \Phi^{(1)}(s) + \Phi^{(2)}(s), \tag{4.4}$$

where

$$\Phi^{(k)}(s) = C^{(k)}(sI-A^{(k)})^{-1}B^{(k)}, \; k = 1,2. \tag{4.5}$$

Example 4.1 The system in Figure 5 (Section 5) is in parallel. The constituent subsystems are depicted in figures 5(a) and 5(b). The transfer function for the "short" branch is $\Phi^{(2)}(s) = \theta_5\theta_{11}/(s+\theta_{11})$. The other branch was discussed earlier (Example 3.1); its transfer function is given in formula (3.18). The transfer function is the sum of its constituent transfer function as given by formula (2.9).

Certain concepts from the theory of directed graphs (e.g., see [15]) are needed. Let D denote the digraph (directed graph) of a compartmental matrix A, i.e., a directed arc is drawn from compartment j to (another) compartment i if and only if $a_{ij} \neq 0$. A sequence from (compartment) j to i

$$\Gamma: j = \nu_0 \to \nu_1 \to \ldots \to \nu_\ell = i$$

exists in D if and only if the product

$$\pi(\Gamma) = a_{\nu_0\nu_1} a_{\nu_1\nu_2} \cdots \nu_{\nu_{\ell-1}\nu_\ell} \neq 0.$$

The integer ℓ is the <u>length</u> of the sequence. A <u>path</u> is a sequence which does not intersect itself, i.e., $\nu_s \neq \nu_t$ if $s \neq t$.

<u>Lemma 4.1</u> Let (A,B,C) be a system (as described in Section 1). Suppose that p is a positive integer such that each path from an input compartment to an output compartment has length $> p$. Then the Markov matrices,

$$M_k = CA^kB = 0,\ k = 0,1,\ldots,p.$$

<u>Proof.</u> The (i,j) entry of M_k is a sum of products of the form $c_{i\nu_0} a_{\nu_0\nu_1} \cdots a_{\nu_{k-1}\nu_k} b_{\nu_k j}$. For $M_k \neq 0$ there must be an input compartment ν_0 and an output compartment ν_k, such that there is a sequence from ν_0 to ν_k of length k. Certainly, there must exist a path from ν_0 to ν_k of length k. Consequently, $k > p$, which is the desired result.

<u>Proposition 4.1</u> Suppose that a system in parallel has the property that the number of compartments $n^{(2)}$, in one constituent, say $(A^{(2)},B^{(2)},C^{(2)})$, is sufficiently small so that each path in the other constituent, $(A^{(1)},B^{(1)},C^{(1)})$, from an input compartment to an output compartment has length $> 2n^{(2)} - 1$. Then each constituent transfer function is uniquely identifiable.

<u>Proof.</u> By the hypothesis and Lemma 4.1,

$$M_k^{(1)} = C^{(1)}(A^{(1)})^k B^{(1)} = 0,\ k = 0,1,\ldots,2n^{(2)} - 1.$$

Since $$M_k = CA^kB = [C^{(1)},C^{(2)}] \begin{bmatrix} (A^{(1)})^k & 0 \\ 0 & (A^{(2)})^k \end{bmatrix} \begin{bmatrix} B^{(1)} \\ B^{(2)} \end{bmatrix}$$

$$= C^{(1)}(A^{(1)})^k B^{(1)} + C^{(2)}(A^{(2)})^k B^{(2)} = M_k^{(1)} + M_k^{(2)},$$

$M_k^{(2)} = M_k$ is uniquely identifiable, $k = 0,1,\ldots,2n^{(2)} - 1$. In view of Lemma 2.2, $\Phi^{(2)}$ is uniquely identifiable and hence $\Phi^{(2)} = \Phi - \Phi^{(1)}$ is also uniquely solvable.

Example 4.2 Let Φ be the transfer function for the system in Figure 5. The "short" branch has one compartment, i.e., $n^{(2)} = 1$, while the length of the path (there is only one) from the input compartment to the output compartment in the larger branch is 4. By Proposition 4.1, each constituent transfer function is uniquely identifiable from Φ. Now $\Phi^{(2)}(s) = \theta_5\theta_{11}/(s+\theta_{11})$ uniquely identifies θ_5 and θ_{11}, while $\theta_4,\theta_6,\theta_7,\theta_8,\theta_9,\theta_{10}$ are identifiable from $\Phi^{(1)}$ (Example 3.1). Notice that all the parameters in Φ are identifiable from Φ, whether or not the irreducibility condition (2.10) is satisfied.

5. Very low density lipoprotein triglycerides

A. Model description

The kinetics of the triglyceride (TG) moiety of plasma very low density lipoproteins (VLDL) in man, as discussed by Zech et al [16], Berman [17] and Beltz et al [18], may be summarized as follows: Radioactively labeled glycerol is injected into the plasma to serve as the glycerol backbone of the TG moiety; the resulting VLDL-TG tracer curve is observed for forty-eight hours. The compartmental model, Figure 3, may be described in parts.

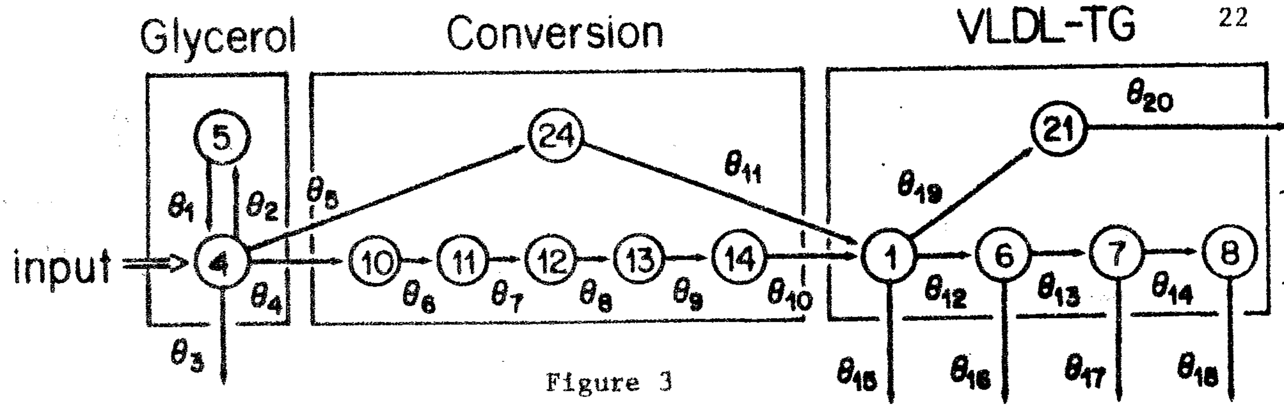

Figure 3

Figure 3. VLDL-TG kinetics. The tracer is injected into compartment 4 (plasma). The observed VLDL-TG tracer curve is $y = x_1+x_6+x_7+x_8+x_{21}$.

The free glycerol precursor subsystem, Figure 4, describes the kinetics of intravenously injected glycerol in plasma. Labeled glycerol, G^*, entering the plasma (compartment 4) equiliberates with the glycerol pool in a two-phase decay process involving extravascular (compartment 5) exchange.

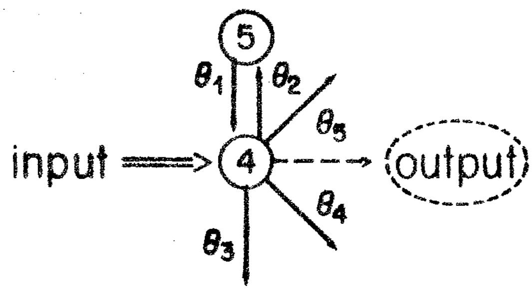

Figure 4. Free glycerol precursor sybsystem. Compartment 4 is observed (indirectly, as a consequence of Lemma 3.5).

Malmendier et el [19] found that about 90% of the glycerol leaving the plasma could be accounted for by conversion to glucose and CO_2 leaving only a small fraction for TG synthesis.

The conversion of glycerol into the TG derivative is an esterification reaction in which three fatty acids attach to a glycerol molecule with loss of H_2O. The incorporation of glycerol into TG follows two pathways as shown in Figure 5. Synthesized TG then reacts with cholesterol and protein to form plasma TG-VLDL.

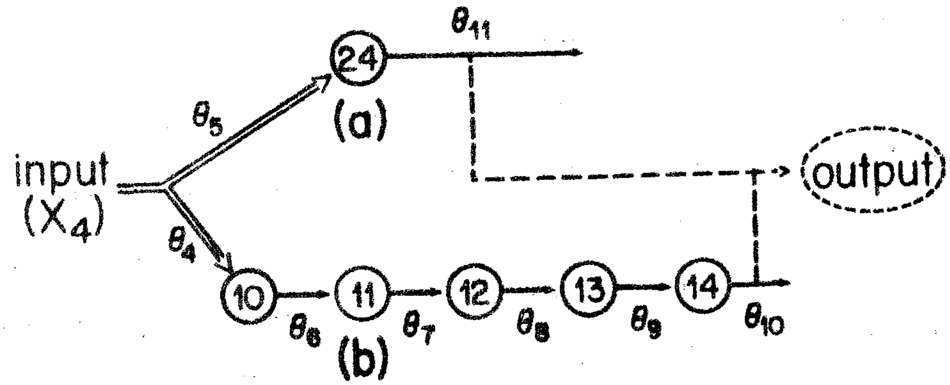

Figure 5. Conversion subsystem: (a) slow conversion pathway, (b) fast conversion pathway. $y = \theta_{10}x_{14} + \theta_{11}x_{24}$ is observed (indirectly, as a consequence of Lemmas 3.4 and 3.5).

Plasma VLDL-TG, Figure 6, consists of a delipidation chain (1,6,7,8) and a single compartment (21), which represents a more slowly catabolized subfraction of VLDL particles. The delipidation chain represents a spectrum of decreasing VLDL-TG particles. Of the triglyceride secreted with the largest particles, a portion is removed during the delipidation, which occurs as the particle gets smaller. The remainder of the particle's TG accompanies it to the next step of the catabolic cascade. The smallest VLDL particles (compartment 8) leaving the delipidation are in the IDL range. The portions removed during delipidation convert back to glycerol and fatty acid. The converted glycerol may recycle through the system, but this recycling has been found to have a negligible effect on the overall kinetics [16] and it has been omitted in more recent discussions of the model [18].

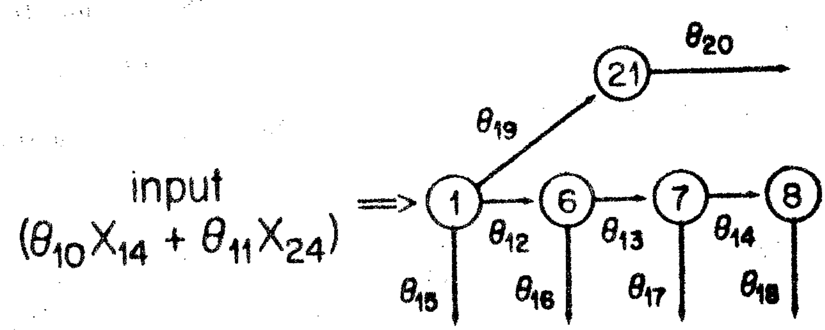

Figure 6. VLDL-TG subsystem. VLDL-TG enters compartment 1. The VLDL-TG curve $y = x_1+x_6+x_7+x_8+x_{21}$ is observed.

B. Structural identification

It is interesting that the decomposition of the total system, Figure 3, for the purpose of structural identification, recovers the same subsystems that were used to construct the model in the first place. The first step of the decomposition is achieved by expressing the system in series, with compartment 1 as the first receiver. The resulting receiver subsystem is the VLDL-TG subsystem, Figure 6, and the transmitter system is the synthesis subsystem, Figure 7.

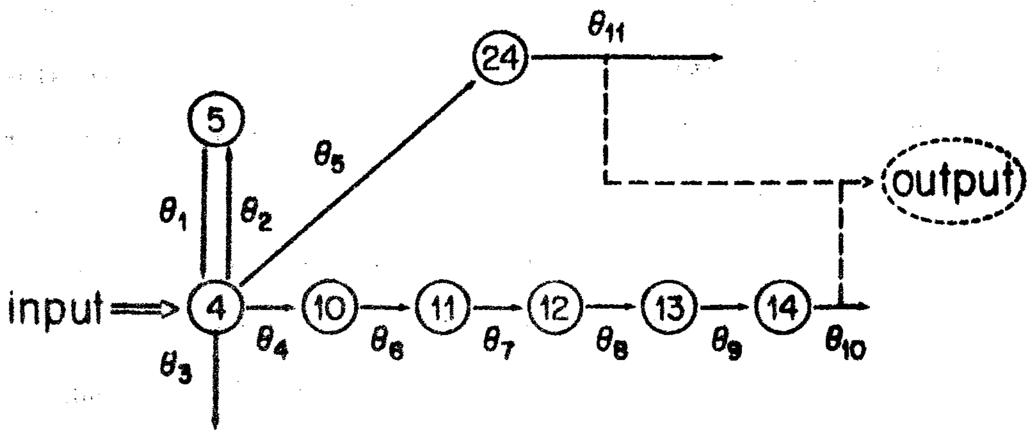

Figure 7. Synthesis subsystem. The input is into compartment 4 and $y = \theta_{10}x_{14} + \theta_{11}x_{24}$ is observed.

The decomposition of the synthesis subsystem, Figure 5, into constituents, Figures 4, 5(a), and 5(b), has already been discussed in Examples 3.2 and 4.1, and it was found (Example 3.3) that the transfer function for the synthesis subsystem, $\Phi^{(S)}$, is a product of the constituent transfer functions given in formulas (2.9) and (2.15). The transfer function for the VLDL-TG subsystem is

$$\Phi^{(V)}(s) = \frac{1}{s+\theta_{12}+\theta_{15}+\theta_{19}}\left\{1 + \frac{\theta_{12}}{s+\theta_{13}+\theta_{16}}\left[1 + \frac{\theta_{13}}{s+\theta_{14}+\theta_{17}}\left(1 + \frac{\theta_{14}}{s+\theta_{18}}\right)\right] + \frac{\theta_{19}}{s+\theta_{20}}\right\}. \tag{5.1}$$

The irreducibility condition for this subsystem is

$$\theta_{20} \notin \{\theta_{13}+\theta_{16}, \theta_{14}+\theta_{17}, \theta_{18}\}, \; \theta_{17} \neq \theta_{18}. \tag{5.2}$$

We recall, from Example 3.3, that the synthesis subsystem is irreducible if and only if conditions (2.10), (3.20) and (3.21) are satisfied. To these we add the conditions which prohibit coincidence between the roots of one constituent transfer function with the zeros of the other; these are:

$$(s+\theta_{13}+\theta_{16})(s+\theta_{14}+\theta_{17})(s+\theta_{18})(s+\theta_{20}) + \theta_{12}(s+\theta_{14}+\theta_{17})(s$$

$$+\theta_{18})(s+\theta_{20}) + \theta_{12}\theta_{13}(s+\theta_{18})(s+\theta_{20}) + \theta_{12}\theta_{13}\theta_{14}(s+\theta_{20})$$

$$+ \theta_{19}(s+\theta_{13}+\theta_{16})(s+\theta_{14}+\theta_{17})(s+\theta_{18}) \neq 0 \quad \text{for}$$

$$s = -\theta_k, \; 6 \leq k \leq 11 \quad \text{or} \quad s = -\pi_i, \; i = 1,2. \tag{5.3}$$

$$\theta_1 \neq \theta_{12} + \theta_{15} + \theta_{17}, \; \theta_{13} + \theta_{16}, \; \theta_{14} + \theta_{17}, \; \theta_{18}, \; \theta_{20}. \tag{5.4}$$

$$(s+\theta_{11})\theta_4 \prod_{k=6}^{10} \theta_k + \theta_6\theta_{11} \prod_{k=1}^{6} (s+\theta_k) \neq 0 \quad \text{for}$$

$$s = -\theta_{12} - \theta_{15} - \theta_{19}, \; -\theta_{13} - \theta_{16}, \; -\theta_{14} - \theta_{17}, \; -\theta_{18}, \; -\theta_{20}. \tag{5.5}$$

Let us assume that all these irreducibility conditions, (2.10), (3.20), (3.22), (5.3), (5.4), and (5.5) are satisfied. Condition (i) in Lemma 3.2 holds because $C^{(V)}B^{(V)} = 1$, ("V" refers to the VLDL-TG subsystem). Thus, by Proposition 3.1, the constituent transfer functions $\Phi^{(V)}$ and $\Phi^{(S)}$ are identifiable. It is not difficult to show that the parameters θ_k, $12 \leq k \leq 20$, are identifiable from $\Phi^{(V)}$; thus, these parameters are identifiable (Lemma 2.3).

Since $\Phi^{(S)}$ is identifiable, its constituent transfer functions $\Phi^{(G)}$ and $\Phi^{(C)}$ are identifiable as shown in Example 3.3 ("G" denotes the free glycerol subsystem and "C" denotes the conversion subsystem). Now

θ_k, $4 \leq k \leq 11$ are identifiable from $\Phi^{(C)}$ (Example 4.2). Moreover, θ_1, θ_2, and $\theta_3 + \theta_4$ are identifiable from $\Phi^{(G)}$ (Example 2.3). Since θ_4 is identifiable, so is θ_3. Thus, the system, Figure 3, is identifiable provided that the irreducibility conditions, given above, are satisfied.

C. Discussion

The main objective of structural identifiability analysis is to ascertain the theoretical limits of the parameter estimation problem. In practice, the estimation of twenty parameters from a single tracer curve is not feasible, even though the data might be free of noise. Usually, thirteen relationships between the parameters are stipulated, a priori, leaving only seven free parameters to be estimated [18].

The irreducibility conditions, (2.10), (3.20), (3.21), (5.3), (5.4), and (5.5), guarantee system identifiability (independent if whether or not a priori relationships are imposed). The fact that the irreducibility conditions are satisfied almost everywhere (see Remark 2.1) may also be deduced from the criteria specified in Remark 3.1. Using Proposition 3.2 in place of Proposition 3.1, we obtain system identifiable in the alost-everywhere sense (without regard to the irreducibilty conditions). The irreducibility conditions may also play a role in the parameter estimation problem (see Remark 3.2).

Figure Captions

Figure 1. Subsystems in series: $\Phi = \phi^{(2)}\phi^{(1)}$.

Figure 2. Subsystems in parallel: $\Phi = \phi^{(1)} + \phi^{(2)}$.

Figure 3. VLDL-TG kinetics. The tracer is injected into compartment 4 (plasma). The observed VLDL-TG tracer curve is $y = x_1+x_6+x_7+x_8+x_{21}$.

Figure 4. Free glycerol percursor subsystem. Compartment 4 is observed (indirectly, as a consequence of Lemma 3.5).

Figure 5. Conversion subsystem: (a) slow conversion pathway, (b) fast conversion pathway. $y = \theta_{10}x_{14} + \theta_{11}x_{24}$ is observed (indirectly, as a consequence of Lemmas 3.4 and 3.5).

Figure 6. VLDL-TG subsystem. VLDL-TG inputs into compartment 1 and $y = x_1+x_6+x_7+x_8+x_{21}$ is observed.

Figure 7. Synthesis subsystem. The input is into compartment 4 and $y = \theta_{10}x_{14} + \theta_{11}x_{24}$ is observed.

REFERENCES

1. R. Bellman amd K. J. Astrom, On structural identifiabililty, Math. Biosci., 7: 329-339.

2. R. F. Brown and J. P. Norton, Identifiability of large compartmental models, Large Scale Systems 3: 159-175 (1982).

3. H. Pohjanpalo and B. Wahlstrom, Software for solving identifications and identifiability problems e.g. in compartmental systems, Mathematics and Computers in Simulation, 24(1982).

4. M. Milanese and N. Sorrentino, Decomposition methods for the identifiability analysis of large systems, Int. J. Control, 28:71-19 (1978).

5. J. Eisenfeld, New techniques for structural identifiability for large linear and nonlinear compartmental systems, Mathematics and Computers in Simulation, 24:494-501 (1982).

6. J. Eisenfeld, On identifiability of inpulse-response in compartmental systems, Math. Biosci., 47:15-23 (1979).

7. C. Cobelli and G. Romanin-Jacur, On the structural identifiability of biological compartmental systems in a general input-output configuration, Math. Biosci., 30: 139-151 (1976).

8. C. Cobelli, A. Lepschy, and G. Romanin-Jacur, Identifiability of compartmental systems and related structural properties, Math. Biosci., 44: 1-18 (1979).

9. C. Cobelli and J. J. Distefano, III, Parameter and structural identifiability concepts and ambiguities: a critical review and analysis, Am. J. Physiol., 239 (Regulatory Integrative Comp. Physiol. 8): R7-R24 (1980).

10. J. A. Jacquez, Compartmental Analysis in Biology and Medicine, Elsevier, Amsterdam, 1972.

11. F. R. Gantmacher, The Theory of Matrices, Chelsea Publ. Co., New York, 1959, Vol. 2: 97-98, 1964.

12. R. W. Brockett, Finite Dimensional Linear Systems, Wiley, New York, 1970.

13. C. T. Chen, Introduction to Linear Systems Theory, Holt, Rinehart, and Winston, New York, 1970.

14. J. Z. Hearon, Theorems on linear systems, Ann. N. Y. Acad. Sci., 108: 36-68 (1963).

15. F. Harary, R. Z. Norman, and D. Cartwright, Structural Models: An Introduction to the Theory of Directed Graphs, Wiley, New York, 1965.

16. L. A. Zech, S. M. Grundy, D. Steinberg, and M. Berman, Kinetic Model for production and Metabolism of very low density lipoprotein triglycerides, J. Clin. Invest., 63: 1262-1273 (1979).

17. M. Berman, Analysis of kinetic data, Prog. Biochem. Pharmacol., 15: 67-108 (1979).

18. W. F. Beltz, S. M. Grundy and T. E. Carew, An efficient program for estimation of kinetic parameters in a model of very low density lipoprotein triglyceride metabolism, in Lipoprotein Kinetics and Modeling, M. Berman, S. M. Grundy and B. Howard (ed's), Academic Press, New York, 1982.

19. C. L. Malmendier, C. Delcroix, and M. Berman, Interrelations in the oxidative metabolism of free fatty acids, glucose, and glycerol in normal and hyperlipermic patients, J. Clin. Invest., 54: 461-476.